PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 31 July 2001 (31.07.01)	
International application No. PCT/US00/28158	**Applicant's or agent's file reference** 4003.001610
International filing date (day/month/year) 12 October 2000 (12.10.00)	**Priority date** (day/month/year) 12 October 1999 (12.10.99)
Applicant AHUJA, Sunil et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

10 May 2001 (10.05.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/US 00/28158

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/70 C12Q1/68 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANG J ET AL: "Allelic variants of human beta-chemokine receptor 5 (CCR5) promoter: evolutionary relationships and predictable associations with HIV-1 disease progression." GENES AND IMMUNITY, vol. 1, no. 1, 1 September 1999 (1999-09-01), pages 20-27, XP001002713 ISSN: 1466-4879	1,2, 12-14, 16-19, 23,24, 26,27
A	the whole document	1-37

X	WO 99 23253 A (BRIEN STEPHEN J O ;US HEALTH (US); WINKLER CHERYL ANN (US)) 14 May 1999 (1999-05-14) page 20, line 21 -page 25, line 16; claims 2-12	1,2, 12-19, 23-27, 33,34

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2001	28/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gabriels, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 09162 A (BRIEN STEPHEN J O ;SMITH MICHAEL (US); US HEALTH (US); CARRINGTON) 25 February 1999 (1999-02-25) claims 15-21	1,2, 12-19, 23,24, 26,27
X	WO 98 05798 A (AARON DIAMOND AIDS RESEARCH CE) 12 February 1998 (1998-02-12) claims 1-6	1,2,12, 13, 16-19, 23,24, 26,27
P,X	GONZALEZ ENRIQUE ET AL: "Race-specific HIV-1 disease-modifying effects associated with CCR5 haplotypes." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 96, no. 21, 12 October 1999 (1999-10-12), pages 12004-12009, XP002168968 Oct. 12, 1999 ISSN: 0027-8424 the whole document	1-37
E	WO 01 12857 A (UAB RESEARCH FOUNDATION) 22 February 2001 (2001-02-22) the whole document	1,2, 12-14, 16-19, 23,24, 26,27

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2; (complete) 12-19,23-27,33,34; (partially)

Invention 1:

Compositions, kits, uses thereof, and methods comprising detecting polymorphisms on both the alleles of the CCR5 and CCR2 genes correlated with the risk of HIV-1 infection or disease progression in humans and methods of treatment derived thereof.

2. Claims: 32; (complete) 3-31,33-37; (partially)

Invention 2:

Compositions, kits, uses thereof, and methods comprising detecting complex human haplotypes of the CCR5 and CCR2 genes associated with the risk of HIV-1 infection or disease progression in humans and methods of treatment derived thereof.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[redacted] Application No
PCT/US 00/28158

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9923253 A	14-05-1999	AU 1120799 A	24-05-1999
WO 9909162 A	25-02-1999	AU 9016298 A	08-03-1999
		EP 1002081 A	24-05-2000
WO 9805798 A	12-02-1998	AU 4055897 A	25-02-1998
		US 6057102 A	02-05-2000
WO 0112857 A	22-02-2001	NONE	

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JSvn/7169		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/28158	12/10/2000	12/10/1999
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/05/2001	20.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Favre, N Telephone No. +49 89 2399 7363

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/28158

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-186 as originally filed

Claims, No.:

1-23 with telefax of 21/10/2001

Drawings, sheets:

1/4-4/4 as originally filed

Sequence listing part of the description, pages:

1-28, as originally filed

1-28, filed with the letter of 05.02.2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 23 with regard to industrial applicability, and 2.

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☒ the claims, or said claims Nos. 2 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 3-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1, 3-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1, 3-22
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

1. Sequence listing pages 1-28 filed with the letter of 02.05.2001 do not form part of the application (Rule 13ter.1(f) PCT).

2. The application as originally filed did not refer to a set of nucleic acid fragments allowing the detection of each of the human haplotype groups depicted in the phylogenetic tree set out in Figure 1B. The subject-matter of amended independent claim 2 filed with the telefax dated 21.10.2001 hence introduces subject-matter which extends beyond the content of the application as originally filed, contrary to the requirements of Article 34(2)(b) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
   Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

2. Independent claim 2 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempts to define the subject-matter in terms of the result to be achieved, i.e. allowing the detection of each of the human haplotype groups depicted in the phylogenetic tree set out in Figure 1B, which merely amounts to a statement of the underlying

problem.

2.1 Moreover, the description neither discloses such an a set of nucleic acid fragments nor provides sufficient information for the skilled person to derive such set without undue burden. Hence, independent claim 2 is not supported by the description in the sense of Article 6 PCT, which description does not meet the requirements of Article 5 PCT, as it does not enable the person skilled in the art to carry out without undue burden the subject-matter of claim 2.

2.2 In view of the above, it is presently not possible to formulate a meaningful opinion on the subject-matter of independent claim 2 with regard to novelty, inventive step and industrial applicability.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. For the assessment of the present claim 23 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. The documents "Proceedings of the National Academy of Sciences USA, 1999, **96**(21):12004-12009" and "WO-A-01 12857" indicated in the search report as P-,

respectively E-documents are not to be regarded as state of the art according to Articles 33(2) and 33(3) PCT, as the date of priority claimed can be allowed for the relevant parts of the present application (see also Item VI).

3. The attention of the applicant is drawn to the fact that the **intended use** of a product is **not a technical feature of the product *per se***. In other words, a claim defining a "product for a particular use" actually defines said product as being "suitable for" said particular use (see the Guidelines C-III, 4.8 *and seq.*).

3.1 Document D1 (Genes and Immunity, 1999, 1:20-27) discloses (cf. abstract, pages 23-26 and Tables 4 and 5) compositions comprising nucleic acid segments that detect a human CCR5 or CCR2 polymorphism. Moreover, as demonstrated in D1, said compositions of D1 are suitable for use in detecting polymorphisms on both CCR5 alleles as well as on both CCR2 alleles of a human subject and for correlating said polymorphisms with the risk of HIV-1 infection or disease progression in humans (e.g. abstract and introduction). Furthermore, D1 discloses said compositions in relation to the polymorphisms corresponding to the alleles HHD (P*0103), HHF (P*0202), HHE (P*0201), HHG*1 and HHG*2 (P*0201), HHA (P*0102) and HHB (P*0102).

Document D2 (WO-A-99 23253) discloses compositions comprising nucleic acid segments that detect a human CCR5 or CCR2 polymorphism. Said compositions of D1 are suitable for use in detecting polymorphisms on both CCR5 alleles as well as on both CCR2 alleles of a human subject and for use in a method for determining the susceptibility of a subject to HIV-1 infection by determining the SDF-1, CCR2, and CCR5 allelic profile (cf. pages 19-20).

Similarly, document D3 (WO-A-99 09162) discloses (e.g. claims 15-21) methods for determining the prognosis of a subject exposed to HIV-1 and a method for determining the susceptibility of a subject to HIV-1 infection by determining the CCR2 and CCR5 allelic profile, wherein said methods are performed using compositions comprising nucleic acid segments that detect a human CCR5 or CCR2 polymorphism.

Finally D4 (WO-A-98 05798) discloses (cf. claims 1-15) methods to detect mutations of the CKR-5 receptor (CCR5) which confer resistance to HIV infection for homozygous individuals, wherein said methods are performed using compositions comprising nucleic acid segments that detect a human CCR5 polymorphism.

3.2 The subject-mater of present independent claim 1 differs from the teachings of D1, which is considered to be the closest prior art document, in that the therein-defined set of nucleic acid segments must be able to recognise 2 additional nucleotides in the promoter of the CCR5 gene at positions 29 and 208 as shown in SEQ ID NO:65, respectively.
According to the applicant, the definition of these two additional positions, when combined with the definition of the amino acid 64 of the CCR2 gene and of the presence or absence of the 32 base pair deletion Δ32 in the open reading frame of the CCR5 gene, allows the determination of CCR5 haplogroups in the worldwide population.
Moreover, according to the applicant, the set of nucleic acid segments as described in D1 fails to clearly identify all the relevant haplotypes, for example P*201 (see Figure 2A of D1) fails to differentiate between HHE, HHG*1 and HHG*2. As illustrated in Figures 4A and 4B of the present application, the distinction between HHE, HHG*1 and HHG*2 is however of importance to determine the influence of the CCR5 haplotype on HIV infections.
Thus, it appears that the set of nucleic acid segments as claimed in present independent claim 1 are more advantageous than those defined in the prior art. None of the prior art documents at hand neither disclose nor fairly suggest to detect all the seven nucleotides defined in present independent claim 1.
The subject-matter of independent claim 1 is therefore considered to be novel and inventive in the sense of Articles 33(2) and 33(3) PCT.

3.3 Dependent claims 3-5 further define specific embodiments of the novel and inventive method of claim 1. Dependent claims 3-5 are hence also considered to meet the requirements of Articles 33(2) and 33(3) PCT.

3.4 The sets of nucleic acid segments defined in present claims 6-8 do not differ from those defined in present claims 1 and 3-5 (see also Item VIII). Therefore, the

above argumentation also applies for the subject-matter of claims 6-8, which are hence also considered to be novel and inventive in the sense of Articles 33(2) and 33(3) PCT.

3.5 Furthermore, the kits defined in claims 9-11, which kits comprise the novel and inventive sets of nucleic acid segments of claim 1 are also considered to meet the requirements of Articles 33(2) and 33(3) PCT.

3.6 In addition, the methods defined in claims 12-23 also refer to the novel and inventive subject-matter of independent claim 1. As a consequence, the subject-matter of claims 12-23 is also considered to be novel and inventive in the sense of Articles 33(2) and 33(3) PCT.

Re Item VI
Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO-A-01 12857	22.02.2001	11.08.2000	12.08.1999*

Should the present application enter the national or regional phase, the above cited document could be relevant for the question of novelty (e.g claims).

*Validity of the claimed priority has not been checked.

Re Item VIII

Certain observations on the international application

1. Independent claim 1 lacks clarity in the sense of Article 6 PCT. This claim refers to CCR5 and merely further refers to an amino acid at position 64 and to a Δ32 mutation. The claim does however not teach as to where these further parameters should be assessed, e.g. amino acid 64 of the **CCR2** gene.

2. Although claims 1, 6 and 7 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult to unambiguously determine the matter for which protection is sought, and thus places an undue burden on others seeking to establish the extent of the protection.
Hence, claims 1, 6 and 7 do not meet the requirements of Article 6 PCT.

2.1 A similar objection also applies for the subject-matter of independent claims 9 and 10, which do not meet the requirements of Article 6 PCT.

2.2 Moreover, present independent claims 12, 13 and 17 also do not meet the requirements of Article 6 PCT for the same reasons as presented under point 2. above.

3. Claim 10 refers to a kit, which is considered to be a composition of substances and/or entities. The claim comprises as an additional feature instructions for the use of the kit components. Such instructions are however considered as characterising a method using the kit, rather than the kit *per se*, and as such obscure the scope of the claim since its category is no longer clear (Article 6 PCT).

4. Claim 13 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result, i.e. the set of nucleic acid segments defined in present claim 1, should be added.

5. The vague and imprecise statement in the description on page 165, lines 11-13, i.e. spirit of the claims, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

CLAIMS:

1. A composition comprising at least a first nucleic acid segment that detects a human CCR5 polymorphism for use in detecting polymorphisms on both CCR5 alleles of a human subject and for correlating polymorphisms on both CCR5 alleles with the risk of HIV-1 infection or disease progression in humans.

2. The composition of claim 1, wherein said composition comprises at least a first nucleic acid primer that detects a human CCR5 polymorphism.

3. The composition of claim 1 or 2, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHE allele of human CCR5.

4. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHC allele of human CCR5.

5. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHF*1 allele of human CCR5.

6. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHD allele of human CCR5.

7. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHG*2 allele of human CCR5.

8. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHA allele of human CCR5.

9. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHB allele of human CCR5.

10. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHF*2 allele of human CCR5.

11. The composition of any preceding claim, wherein said composition comprises at least a first nucleic acid segment or primer that detects an HHG*1 allele of human CCR5.

12. The composition of any preceding claim, wherein said composition comprises at least a first and second nucleic acid segment or primer that each detect a distinct human CCR5 polymorphism.

13. The composition of any preceding claim, wherein said composition comprises a plurality of nucleic acid segments or primers that detect distinct human CCR5 polymorphisms.

14. The composition of any preceding claim, wherein said composition further comprises at least a first nucleic acid segment or primer that detects a human CCR2 polymorphism at both alleles.

15. The composition of any preceding claim, wherein said composition further comprises at least a first and second nucleic acid segment or primer that each detect a distinct human CCR2 polymorphism at both alleles.

16. Use of a composition in accordance with any preceding claim in the preparation of a diagnostic formulation for determining the genotype of a human subject at the CCR5 locus indicative for HIV-1 infection or disease progression.

17. Use of a composition in accordance with any preceding claim in the preparation of a diagnostic formulation for identifying a human subject at increased risk of HIV-1 infection.

18. Use of a composition in accordance with any one of claims 1 through 15 in the preparation of a prognostic formulation for identifying a human subject at increased risk of HIV-1 disease progression.

19. Use of a composition in accordance with any one of claims 1 through 15 in the preparation of a medicinal test kit for identifying a human subject with increased risk of HIV-1 infection or disease progression.

20. Use according to any one of claims 16 through 19, wherein said human subject is a Caucasian and wherein the presence of two HHE alleles of CCR5 is indicative of an increased risk of HIV-1 infection or disease progression.

21. Use according to any one of claims 16 through 19, wherein said human subject is an African-American and wherein the presence of an HHC and an HHF*1 allele, an HHC and an HHE allele, two HHC alleles, or an HHC and an HHD allele of CCR5 is indicative of an increased risk of HIV-1 infection or disease progression.

22. Use according to any one of claims 16 through 19, wherein said human subject is a child and wherein the presence of an HHC and an HHE allele, two HHE alleles, or an HHE allele and an HHG*2 allele of CCR5 is indicative of an increased risk of HIV-1 infection or disease progression.

23. A kit comprising at least a first composition in accordance with any one of claims 1 through 15.

24. The kit of claim 23, wherein said kit further comprises instructions for detecting polymorphisms on both CCR5 alleles of a human subject and for correlating polymorphisms on both CCR5 alleles with the risk of HIV-1 infection or disease progression in humans.

25. The kit of claim 23, further comprising at least a first anti-viral therapeutic agent.

26. A method of assessing the risk of a human subject for HIV-1 infection or disease progression, comprising identifying the genotype of both CCR5 alleles of said subject using a composition in accordance with any one of claims 1 through 15.

27. A method of assessing the risk of a human subject for HIV-1 infection or disease progression, comprising identifying the genotype of both CCR5 alleles of said subject, wherein the genotype of both CCR5 alleles is indicative of the risk of said subject for HIV-1 infection or disease progression.

28. The method of claim 27, wherein said human subject is a Caucasian, and the presence of two HHE alleles of CCR5 is indicative of an increased risk of HIV-1 infection or disease progression.

29. The method of claim 27, wherein said human subject is an African-American, and the presence of an HHC and an HHF*1 allele, an HHC and an HHE allele, two HHC alleles, or an HHC and an HHD allele of CCR5 is indicative of an increased risk of HIV-1 infection or disease progression.

30. The method of claim 27, wherein said human subject is a child, and the presence of an HHC and an HHE allele, two HHE alleles, or an HHE allele and an HHG*2 allele of CCR5 is indicative of an increased risk of HIV-1 infection or disease progression.

31. The method of claim 27, wherein said method further comprises identifying the genotype of a CCR2 allele of said subject, wherein the genotype of a CCR2 allele is further indicative of the risk of said subject for HIV-1 infection or disease progression.

32. A method of identifying a child at increased risk for transmission of an HIV-1 virus, comprising identifying the genotype of both CCR5 alleles of said child, wherein the presence of an HHC and an HHE allele, two HHE alleles, or an HHE allele and an HHG*2 allele of CCR5 is indicative of an increased risk of transmission of said HIV-1 virus.

33. A method of reducing HIV-1 infection or disease progression in a human subject, comprising identifying a susceptible human subject by determining the genotype of both CCR5 alleles of said subject using a composition in accordance with any one of claims 1 through 15; and treating said susceptible human subject with a biologically effective amount of at least a first anti-viral agent.

34. A method of reducing HIV-1 infection or disease progression in a human subject, comprising:

(a) determining the genotype of both CCR5 alleles of said human subject, thereby identifying a susceptible human subject at increased risk of HIV-1 infection or disease progression; and

(b) treating said susceptible human subject with a biologically effective amount of at least a first anti-viral agent.

35. The method of claim 34, wherein said human subject is Caucasian, and the presence of two HHE alleles of CCR5 is indicative of a susceptible human subject at increased risk of HIV-1 infection or disease progression.

36. The method of claim 34, wherein said human subject is African-American, and the presence of an HHC and an HHF*1 allele, an HHC and an HHE allele, two HHC alleles, or an HHC and an HHD allele of CCR5 is indicative of a susceptible human subject at increased risk of HIV-1 infection or disease progression.

37. The method of claim 34, wherein said human subject is a child, and the presence of an HHC and an HHE allele, two HHE alleles, or an HHE allele and an HHG*2 allele of CCR5 is indicative of a susceptible human subject at increased risk of HIV-1 infection or disease progression.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SILVERSTON, Judith
ABEL & IMRAY
20 Red Lion Street
London WC1R 4PQ
GRANDE BRETAGNE

ABEL & IMRAY
CASE NO. 7169
G.O. MA
24 DEC 2001
A/C? Y N
CPA? Y N COPIED

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.12.2001
Applicant's or agent's file reference: JSvn/7169	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/28158	12/10/2000	12/10/1999

Applicant
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM

DOCKETED ☐ UP...
Previously ✓ Not Req...
Appl. Info.
Reg/Grant Info
Action Required IPEA...
By

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Digiusto, M Tel.+49 89 2399-8162

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
JSvn/7169		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/28158	12/10/2000	12/10/1999
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/05/2001	20.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Favre, N Telephone No. +49 89 2399 7363

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/28158

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-186 as originally filed

Claims, No.:

1-23 with telefax of 21/10/2001

Drawings, sheets:

1/4-4/4 as originally filed

Sequence listing part of the description, pages:

1-28, as originally filed

1-28, filed with the letter of 05.02.2001

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 23 with regard to industrial applicability, and 2.

because:

☒ the said international application, or the said claims Nos. 23 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 2 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☒ the claims, or said claims Nos. 2 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1, 3-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1, 3-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1, 3-22
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

1. Sequence listing pages 1-28 filed with the letter of 02.05.2001 do not form part of the application (Rule 13ter.1(f) PCT).

2. The application as originally filed did not refer to a set of nucleic acid fragments allowing the detection of each of the human haplotype groups depicted in the phylogenetic tree set out in Figure 1B. The subject-matter of amended independent claim 2 filed with the telefax dated 21.10.2001 hence introduces subject-matter which extends beyond the content of the application as originally filed, contrary to the requirements of Article 34(2)(b) PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claim 23 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.
   Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(i) PCT).

2. Independent claim 2 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempts to define the subject-matter in terms of the result to be achieved, i.e. allowing the detection of each of the human haplotype groups depicted in the phylogenetic tree set out in Figure 1B, which merely amounts to a statement of the underlying

problem.

2.1 Moreover, the description neither discloses such an a set of nucleic acid fragments nor provides sufficient information for the skilled person to derive such set without undue burden. Hence, independent claim 2 is not supported by the description in the sense of Article 6 PCT, which description does not meet the requirements of Article 5 PCT, as it does not enable the person skilled in the art to carry out without undue burden the subject-matter of claim 2.

2.2 In view of the above, it is presently not possible to formulate a meaningful opinion on the subject-matter of independent claim 2 with regard to novelty, inventive step and industrial applicability.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. For the assessment of the present claim 23 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

2. The documents "Proceedings of the National Academy of Sciences USA, 1999, **96**(21):12004-12009" and "WO-A-01 12857" indicated in the search report as P-,

respectively E-documents are not to be regarded as state of the art according to Articles 33(2) and 33(3) PCT, as the date of priority claimed can be allowed for the relevant parts of the present application (see also Item VI).

3. The attention of the applicant is drawn to the fact that the **intended use** of a product is **not a technical feature of the product *per se***. In other words, a claim defining a "product for a particular use" actually defines said product as being "suitable for" said particular use (see the Guidelines C-III, 4.8 *and seq.*).

3.1 Document D1 (Genes and Immunity, 1999, **1**:20-27) discloses (cf. abstract, pages 23-26 and Tables 4 and 5) compositions comprising nucleic acid segments that detect a human CCR5 or CCR2 polymorphism. Moreover, as demonstrated in D1, said compositions of D1 are suitable for use in detecting polymorphisms on both CCR5 alleles as well as on both CCR2 alleles of a human subject and for correlating said polymorphisms with the risk of HIV-1 infection or disease progression in humans (e.g. abstract and introduction). Furthermore, D1 discloses said compositions in relation to the polymorphisms corresponding to the alleles HHD (P*0103), HHF (P*0202), HHE (P*0201), HHG*1 and HHG*2 (P*0201), HHA (P*0102) and HHB (P*0102).

Document D2 (WO-A-99 23253) discloses compositions comprising nucleic acid segments that detect a human CCR5 or CCR2 polymorphism. Said compositions of D1 are suitable for use in detecting polymorphisms on both CCR5 alleles as well as on both CCR2 alleles of a human subject and for use in a method for determining the susceptibility of a subject to HIV-1 infection by determining the SDF-1, CCR2, and CCR5 allelic profile (cf. pages 19-20).

Similarly, document D3 (WO-A-99 09162) discloses (e.g. claims 15-21) methods for determining the prognosis of a subject exposed to HIV-1 and a method for determining the susceptibility of a subject to HIV-1 infection by determining the CCR2 and CCR5 allelic profile, wherein said methods are performed using compositions comprising nucleic acid segments that detect a human CCR5 or CCR2 polymorphism.

Finally D4 (WO-A-98 05798) discloses (cf. claims 1-15) methods to detect mutations of the CKR-5 receptor (CCR5) which confer resistance to HIV infection for homozygous individuals, wherein said methods are performed using compositions comprising nucleic acid segments that detect a human CCR5 polymorphism.

3.2 The subject-mater of present independent claim 1 differs from the teachings of D1, which is considered to be the closest prior art document, in that the therein-defined set of nucleic acid segments must be able to recognise 2 additional nucleotides in the promoter of the CCR5 gene at positions 29 and 208 as shown in SEQ ID NO:65, respectively.
According to the applicant, the definition of these two additional positions, when combined with the definition of the amino acid 64 of the CCR2 gene and of the presence or absence of the 32 base pair deletion Δ32 in the open reading frame of the CCR5 gene, allows the determination of CCR5 haplogroups in the worldwide population.
Moreover, according to the applicant, the set of nucleic acid segments as described in D1 fails to clearly identify all the relevant haplotypes, for example P*201 (see Figure 2A of D1) fails to differentiate between HHE, HHG*1 and HHG*2. As illustrated in Figures 4A and 4B of the present application, the distinction between HHE, HHG*1 and HHG*2 is however of importance to determine the influence of the CCR5 haplotype on HIV infections.
Thus, it appears that the set of nucleic acid segments as claimed in present independent claim 1 are more advantageous than those defined in the prior art. None of the prior art documents at hand neither disclose nor fairly suggest to detect all the seven nucleotides defined in present independent claim 1.
The subject-matter of independent claim 1 is therefore considered to be novel and inventive in the sense of Articles 33(2) and 33(3) PCT.

3.3 Dependent claims 3-5 further define specific embodiments of the novel and inventive method of claim 1. Dependent claims 3-5 are hence also considered to meet the requirements of Articles 33(2) and 33(3) PCT.

3.4 The sets of nucleic acid segments defined in present claims 6-8 do not differ from those defined in present claims 1 and 3-5 (see also Item VIII). Therefore, the

above argumentation also applies for the subject-matter of claims 6-8, which are hence also considered to be novel and inventive in the sense of Articles 33(2) and 33(3) PCT.

3.5 Furthermore, the kits defined in claims 9-11, which kits comprise the novel and inventive sets of nucleic acid segments of claim 1 are also considered to meet the requirements of Articles 33(2) and 33(3) PCT.

3.6 In addition, the methods defined in claims 12-23 also refer to the novel and inventive subject-matter of independent claim 1. As a consequence, the subject-matter of claims 12-23 is also considered to be novel and inventive in the sense of Articles 33(2) and 33(3) PCT.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim, (day/month/year)*
WO-A-01 12857	22.02.2001	11.08.2000	12.08.1999*

Should the present application enter the national or regional phase, the above cited document could be relevant for the question of novelty (e.g claims).

*Validity of the claimed priority has not been checked.

Re Item VIII

Certain observations on the international application

1. Independent claim 1 lacks clarity in the sense of Article 6 PCT. This claim refers to CCR5 and merely further refers to an amino acid at position 64 and to a Δ32 mutation. The claim does however not teach as to where these further parameters should be assessed, e.g. amino acid 64 of the **CCR2** gene.

2. Although claims 1, 6 and 7 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter. The aforementioned claims therefore lack conciseness. Moreover, lack of clarity of the claims as a whole arises, since the plurality of independent claims makes it difficult to unambiguously determine the matter for which protection is sought, and thus places an undue burden on others seeking to establish the extent of the protection.
   Hence, claims 1, 6 and 7 do not meet the requirements of Article 6 PCT.

2.1 A similar objection also applies for the subject-matter of independent claims 9 and 10, which do not meet the requirements of Article 6 PCT.

2.2 Moreover, present independent claims 12, 13 and 17 also do not meet the requirements of Article 6 PCT for the same reasons as presented under point 2. above.

3. Claim 10 refers to a kit, which is considered to be a composition of substances and/or entities. The claim comprises as an additional feature instructions for the use of the kit components. Such instructions are however considered as characterising a method using the kit, rather than the kit *per se*, and as such obscure the scope of the claim since its category is no longer clear (Article 6 PCT).

4. Claim 13 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result, i.e. the set of nucleic acid segments defined in present claim 1, should be added.

5. The vague and imprecise statement in the description on page 165, lines 11-13, i.e. spirit of the claims, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them (see also the PCT Guidelines, III-4.3a).

CLAIMS

1. A set of nucleic acid segments for identifying the CCR5 haplotype group of both alleles of a human subject, which set comprises at least one nucleic acid segment capable of detecting each of the following haplotype groups, each haplogroup being defined in terms of the nucleotides at positions 29, 208, 303, 627, 630, 676 and 927 of the human CCR5 sequence as shown in SEQ.ID.NO.:65, with definition of the amino acid at position 64 and the presence or absence of the Δ32 deletion, as follows:

Haplogroup	Nucleotide position in CCR5 sequence 29 208 303 627 730 676 927							
HHA:	A	G	G	T	C	A	C	
HHB:	A	T	G	T	C	A	C	
HHC:	A	T	G	T	C	G	C	
HHD:	A	T	G	T	T	A	C	
HHE:	A	G	A	C	C	A	C	
HHF*1:	A	G	A	C	C	A	T	
HHF*2:	A	G	A	C	C	A	T	isoleucine at amino acid 64
HHG*1:	G	G	A	C	C	A	C	
HHG*2:	G	G	A	C	C	A	C	has Δ32, 32 base pair deletion

2. A set of nucleic acid segments for identifying the CCR5 haplotype group of both alleles of a human subject, which set comprises at least one nucleic acid segment capable of detecting each of the human haplotype groups described in the phylogenetic tree set out in Figure 1B.

3. A set of nucleic acid segments as claimed in claim 1 or claim 2, which further comprises at least one nucleic acid segment capable of detecting a human CCR2 polymorphism at both alleles.

4. A set of nucleic acid segments as claimed in claim 3, which comprises at least a first and a second nucleic acid segment that is each capable of detecting a distinct human CCR2 polymorphism at both alleles.

5. A set of nucleic acid segments as claimed in any one of claims 1 to 4, each segment being a primer.

6. A nucleic acid segment for identifying a CCR5 haplotype group of a human subject, which nucleic acid segment is capable of detecting the human haplotype group HHD, which has nucleotide A at position 29, T at position 208, G at position 303, T at position 627, T at position 630, A at position 676 and C at position 927 of the human CCR5 sequence as shown in SEQ.ID.NO.:65.

7. A set of nucleic acid segments for identifying the CCR5 haplotype group of both alleles of a human subject, which set comprises a nucleic acid segment as claimed in claim 6.

8. A set of nucleic acid segments as clamed in claim 7, wherein each nucleic acid segment is a primer.

9. A kit comprising a set of nucleic acid segments as claimed in any one of claims 1 to 5, 7 and 8, or a nucleic acid segment as claimed in claim 6, and further components for carrying out the identification of the CCR5 haplogroup(s).

10. A kit comprising a set of nucleic acid segments as claimed in any one of claims 1 to 5, 7 and 8, or a nucleic acid segment as claimed in claim 6, further comprising instructions for identifying the CCR5 haplotype group of both alleles of a human subject and for correlating the haplogroups on both CCR5 alleles with the risk of HIV-1 infection or disease progression in humans, and which optionally further comprises further components for carrying out the identification of the CCR5 haplogroup(s).

11. A kit as claimed in claim 9 or claim 10, wherein the kit comprises a restriction endonuclease.

12. A method which comprises identifying the CCR5 haplotype group of both alleles of a human subject using a set of nucleic acid segments as claimed in any one of claims 1 to 5, 7 and 8, or a nucleic acid segment as claimed in claim 6.

13. A method comprising identifying the CCR5 haplotype group of both alleles of each member of a cohort of human subjects of a chosen population, the human CCR5 haplotype groups being as defined in claim 1 or as described in Figure 1B, and determining the correlation of the pairs of haplotype groups with risk of HIV-1 infection, transmission or disease progression in that population.

14. A method as claimed in claim 13, wherein the population is an ethnic group.

15. A method as claimed in claim 13 or claim 14, wherein the population is children.

16. A method as claimed in any one of claims 13 to 15, wherein human CCR2 polymorphisms at both alleles are also identified and correlated with risk of HIV-1 infection, transmission or disease progression in that population.

17. A method of assessing the risk of a human subject for HIV-1 infection, transmission or disease progression, comprising identifying the CCR5 haplotype group of both alleles of the human subject using a set of nucleic acid segments as claimed in any one of claims 1 to 5, 7 and 8, or a nucleic acid segment as claimed in claim 6, and correlating the pair of haplogroups identified with the risk of HIV-1 infection, transmission or disease progression associated with that pair of haplogroups.

18. A method as claimed in claim 17, wherein the pair of haplogroups identified for the human subject is correlated with the risk of HIV-1 infection, transmission or disease

progression associated with that pair of haplogroups for a population to which the subject belongs.

19. A method as claimed in claim 18, wherein the correlation between haplogroup pairs and risk of HIV-1 infection, transmission or disease progression has been determined as claimed in any one of claims 13 to 16.

20. A method as claimed in claim 18, wherein the human subject is Caucasian and the presence of two HHE alleles as defined in claim 1 is indicative of an increased risk of HIV-1 infection or disease progression.

21. A method as claimed in claim 18, wherein the human subject is African-American and the presence of an HHC and an HHF*1 haplogroup, an HHC and an HHE haplogroup, two HHC haplogroups, or an HHC and an HHD haplogroup, the haplogroups being as defined in claim 1, is indicative of an increased risk of HIV-1 infection or disease progression.

22. A method as claimed in claim 18, wherein the human subject is a child and the presence of an HHC and an HHE haplogroup, two HHE haplogroups, or an HHE haplogroup and an HHG*2 haplogroup, the haplogroups being as defined in claim 1, is indicative of an increased risk of HIV-1 transmission, infection or disease progression.

23. A method of reducing HIV-1 infection, transmission or disease progression in a human subject comprising identifying a susceptible human subject by a method as claimed in any one of claims 17 to 22 and treating a susceptible human subject with a biologically effective amount of at least a first anti-viral agent.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
4003.001610		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 28158	12/10/2000	12/10/1999
Applicant		
BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1C-1D

[X] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2; (complete) 12-19,23-27,33,34; (partially)

   Invention 1:

   Compositions, kits, uses thereof, and methods comprising detecting polymorphisms on both the alleles of the CCR5 and CCR2 genes correlated with the risk of HIV-1 infection or disease progression in humans and methods of treatment derived thereof.

2. Claims: 32; (complete) 3-31,33-37; (partially)

   Invention 2:

   Compositions, kits, uses thereof, and methods comprising detecting complex human haplotypes of the CCR5 and CCR2 genes associated with the risk of HIV-1 infection or disease progression in humans and methods of treatment derived thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/28158

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/70 C12Q1/68 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TANG J ET AL: "Allelic variants of human beta-chemokine receptor 5 (CCR5) promoter: evolutionary relationships and predictable associations with HIV-1 disease progression." GENES AND IMMUNITY, vol. 1, no. 1, 1 September 1999 (1999-09-01), pages 20-27, XP001002713 ISSN: 1466-4879	1,2, 12-14, 16-19, 23,24, 26,27
A	the whole document	1-37

X	WO 99 23253 A (BRIEN STEPHEN J O ;US HEALTH (US); WINKLER CHERYL ANN (US)) 14 May 1999 (1999-05-14) page 20, line 21 -page 25, line 16; claims 2-12	1,2, 12-19, 23-27, 33,34

	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 June 2001	28/06/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gabriels, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/28158

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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